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MYXŒDEMA AND EXOPHTHALMIC GOITRE IN SISTERS, WITH REMARKS ON THE SYMPTOMATOLOGY OF THE LATTER DISEASE.[1]

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THE occurrence of exophthalmic goitre and myxœdema in members of the same family has been observed by Arthur Maude,[2] whose cases, as far as I can ascertain, are the only ones on record. The following cases have recently been under observation at the Medical Clinic, and Prof. Osler has kindly asked me to report them:

CASE I.—Miss A., aged 19, admitted January 26, 1894, complaining of goitre and great nervousness.

Family History.—The father living and healthy; several brothers living and healthy; her mother is dead; cause unknown. There is no history of tuberculosis, carcinoma, or nervous diseases. She thinks that several members of her family have had "Bright's disease." Her sister is Mrs. B., Case II.

Personal History.—She had measles and scarlet fever when young. The catamenia have never been very regular, and have appeared only once in the last year.

The present illness began about three years ago. After a severe fright she became very nervous, and has been easily excited ever since. The heart has been beating very rapidly, and for about eighteen months enlargement of the thyroid and exophthalmos have been noticed. The voice has been husky of late; the hands tremble, especially on excitement.

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[1] From Prof. Osler's Medical Clinic Johns-Hopkins Hospital.

[2] Maude, St. Bartholomew Hospital Report, 1893.

The appetite is good; there is no nausea or vomiting; the bowels are regular. There is no cough or pain in chest, but she has attacks of dyspnœa.

Status Præsens.—Fairly nourished, slightly built, face markedly flushed, numerous areas of transient flushing on skin. Lips and mucous membranes of good color; tongue clean.

Marked double exophthalmos; no v. Græfe's sign.

Thyroid gland much enlarged symmetrically.

Pulse very rapid, varying from 100 to 140.

Lungs and abdomen negative.

Heart.—Apex heat in sixth space, very powerful and heaving; the sounds are loud, first is booming, second both loud and clear; no murmurs.

Fine tremor of fingers.

Urine negative; no sugar.

The patient was given the dried thyroid extract, gr. v. t. i. d. during her entire stay at the hospital—fourteen days. She neither improved nor became worse, but lost two and a half pounds in weight; pulse remained about the same. She left the hospital on February 9, 1894.

Her physician, Dr. H. B. Melvin, writes that she had to discontinue the thyroid, because of the increase of nervousness. She has been taking tinct. belladonna m xv., t. i. d. for two months, and has improved somewhat. In the last six weeks she has taken it very irregularly. On November 22, 1894, the goitre was much smaller, and the exophthalmos less marked. She is, however, very irritable and does not obey orders.

CASE II.—Mrs. B., sister of Miss A., aged 37, multipara.

Personal History.—She has always been healthy; has never had rheumatism or chorea.

Present illness began about three years ago, after nursing two children with measles, when she was pregnant. Some three months after birth of the child, she noticed that about two days before the menstrual period, the whole body would become more or less swollen, though never pitting on pressure; this would disappear when the menstrual flow began. During the past year the menstrual periods have appeared at about six to eight weeks interval, and the swelling has always been more or less present, though worse at some times than others. The swelling never pits on pressure. Lately she has noticed that the skin has become dry, harsh and rough. She has also lost some hair lately. She always feels chilly. The appetite is good; the bowels are constipated. She is very talkative.

Status Præsens.—A woman of moderate height, but giving the impression of being very large. The face has a heavy, dull look; the cheeks and neck are very full, almost œdematous in appearance. The face is somewhat expressionless, and complexion has rather a doughy character. The supraclavicular spaces are markedly full, though there is no distinct puffiness. The arms and legs are decidedly swollen, though not pitting anywhere, the skin having a resistant feel and being everywhere dry, and in places showing a scaling of the epidermis. The finger nails are thin and show marked longitudinal striations; edges are slightly everted and show irregularities. The hair is dry and coarse.

The thyroid gland could not be felt; owing to the thickness of the neck the palpation was unsatisfactory.

The abdominal and thoracic viscera are negative.

The patient was given thyroid, gr. v., t. i. d., which in a week was reduced to gr. v., b. d. She at once began to improve. Her weight while in the hospital—fourteen days—went down from 189 to 178.5 pounds, and in the twenty-five days after leaving the hospital she lost almost as many pounds. Her pulse on admission was 60 to 70, and on discharge it was 80 to 100. She looked much brighter and felt better.

Her physician, Dr. Melvin, writes November 22, 1894, that she has steadily improved; she is now taking only three grains every other day. She is eight months pregnant, and it is interesting that, while in previous pregnancies she was very nauseated, this symptom is absent in the present one. The amount of the thyroid extract could not be decreased during pregnancy.

These cases are of especial interest in the bearing on the question of the pathogenesis of exophthalmic goitre. Although the disease has been well known for fifty years, and studied with especial care of late, there is still much difference of opinion as to its cause. The symptoms, for which any theory must account, have become more and more detailed, and are increasing constantly, until now exophthalmic goitre has one of the most complex symptomatologies.

The disease occurs much oftener in women than in men, probably about twelve to one, though the estimates vary. It occurs oftenest in early and middle adult life, but cases have been reported in children and in persons over sixty years of age.

Many cases of heredity are in the literature. Hector Mackenzie[3] in forty cases, had five in whose family there was exophthalmic goitre. In Bull's case a mother and two sisters were affected. Oesterreicher reports the most remarkable instance; an hysterical woman had ten children, eight of whom had exophthalmic goitre; one of these children had four daughters with exophthalmic goitre. Arthur Maude[1] reports a case of a woman with myxœdema, whose daughter had exophthalmic goitre.

In addition there is frequently a neuropathic family history. The English have laid stress on rheumatism and quinsy.

The immediate cause may be some violent emotion, such as in Case I., but in many cases the history is negative.

There is the well-known classical triad of symptoms; exophthalmos, goitre, and tachycardia. In connection with the exophthalmos there are certain changes in the motions of the lids; v. Graefe's sign, inability of the upper lid to follow the downward movement of the eyeball. This sign is much less common than is generally supposed. It was not present in one of the hospital cases, seventeen in number. On the other hand, Sharkey[4] found it in about two per cent. of 613 cases of other diseases, and maintained it could be produced by steady staring in a perfectly normal person. Stellwag's sign (observed already in 1849 by White Cooper) is a widening of the palpebral fissure, owing to spasmodic retraction of the upper lid. In connection with this the patient winks less frequently than normally. This is much more constant than v. Graefe's sign. Occasionally retraction of the lower lid is seen, and still more rarely ptosis.

The ocular muscles are at times involved. Möbius's sign consists of a lack of convergence of the two eyes. Not only do they not converge on a close object, he says, but often one eye turns out instead of in. He believes this is only a symptom of the general weakness, as convergence requires more nervous strain than other co-ordinated movements. External ophthalmoplegia has been often noted, as well as other affections of the ocular muscles.

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[3] Mackenzie, *Lancet*, 1890, ii., 545.

[4] Sharkey, *Lancet*, 1890, ii., 877.

A fourth cardinal symptom has been added to the classical triad—the tremor. It was described in detail and given its full clinical value by Pierre Marie. It is involuntary, fine, and rapid (eight to the second). It oftenest affects the hands and arms, but at times the head and lower limbs. It may become coarse and violent, but in those cases hysteria is always to be suspected. It is one of the most constant symptoms, and is of great value in the diagnosis of the "masked" cases (*formes frustes*).

The appetite varies from anorexia to bulimia, and is at times perverted. Vomiting is at times a most distressing and often fatal symptom. It may be pernicious, and post-mortem, no gastric condition to account for it is to be found There is often a paroxysmal diarrhœa, a true intestinal crisis, aptly termed "bowel hurry" by Hingston Fox. It lasts but twenty-four to forty-eight hours, and then disappears for a time. It may, however, be constant. In one of our cases it was of the "morning diarrhœa" type of Lauder Brunton; four or five loose stools soon after breakfast, and no more for the rest of the day.

There is usually polypnœa, but no dyspnœa, unless from pressure by the goitre. Associated with this is a short, dry cough, and occasionally hæmoptysis. This, with the emaciation seen in exophthalmic goitre, has often given rise to the diagnosis of tuberculosis. Dr. Bryson has called attention to diminished chest expansion, but this has not been generally confirmed.

The voice often becomes high-pitched and nasal. In some acute cases (Mueller and Koeppen) it was nasal, monotonous, and very weak.

There is polyuria, and occasionally glycosuria and albuminuria. Boinet and Silbert[5] have isolated three ptomaines from the urine, which, injected into animals, caused convulsive symptoms, but nothing like exophthalmic goitre. Gilles de la Tourette has found the usual constituents unchanged.

Fever is often present, usually only slight, but may be very high (Bertoye). It is interesting that in this fever the urine remains unchanged.

The skin is usually moist and reacts quickly; in one case the prick of a pin caused a general sweat. Profuse sweats and subjective flushes are common. Vigouroux has shown that the electrical resistance is decreased. This has been confirmed, especially by Eulenburg and Kahler, but it is also present in neurotic subjects without exophthalmic goitre.

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[5] Boinet and Silbert, *Rev. de Med.*, January, 1892.

There is often some pigmentation of the skin. It varies from a dirty grey to a mulatto brown (in Oppenheim's[6] case). Burton[7] remarked that the deep pigmentation is most marked at pressure points, as at the waist, under garters, under a ring, etc. The pigmentation may be so intense as to simulate Addison's disease.

Other skin affections have been observed; vitiligo, eczemas, urticaria, scleroderma, jaundice.

There are nervous symptoms aside from the tumor. Paresis of almost every muscle has been seen. Especially common is the paraparesis of the legs (the "giving way of the legs"), on which Charcot laid great stress. Atrophy of some muscles has occurred. Muscular cramps are not uncommon, and Maude and Chvostek have called attention to choreiform movements. Joffroy[8] has lately brought out a sign—paresis of the frontalis. The patient is requested to look down, and then, without raising the head, is to look at the ceiling. A normal individual will wrinkle his forehead, but in exophthalmic goitre the forehead remains smooth. This is not present in all cases and is to be seen in some hysterical patients.

Undoubtedly many of these pareses are hysterical, but according to Joffroy there is a true "Basedowian paresis."

Œdema has been especially noted by Moebius[9] and Maude. It does not necessarily occur in dependent portions; in a case of Moebius's it increased from below upwards, being most marked just below the umbilicus. It often comes on suddenly and resembles angioneurotic œdema.

Non-pitting, hard, œdematous areas have also been seen. Hektoen, of Chicago, lately had a case in which there was a solitary patch of this below the knee.

In a few cases (Sollier, Kowalewsky, v. Jaksch), there has been true myxœdema associated with exophthalmic goitre, so that the above may be a transition stage.

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[6] Oppenheim, *Berlin Klin. Wochenschr.*, May 7, 1888.

[7] Burton, *Lancet*, 1888, ii., 573.

[8] Joffroy, *Progrès Méd.*, December 23, 1893; January 27th, March 24th, March 31, 1894.

[9] Moebius, *Schmidt's Jahrbücher*, ccxxx., 185.

The mental condition is nearly always changed, generally in the direction of exaltation. From mere irritability and "nervousness" up to a violent mania, all gradations have been observed. Melancholia, delire de toucher, arithmomania, and various delusions are occasionally present.

Exophthalmic goitre has been associated with various diseases of the nervous system: tabes dorsalis, epilepsy, paralysis agitans, hereditary chorea, syringomyelia, but oftenest with hysteria. Diabetes is occasionally present, though a pure glycosuria is much more frequent. These all seem to be more concomitants than true complications, and when autopsies have been made the lesions of the nervous disease were, apparently, unmodified by the exophthalmic goitre.

There is often great emaciation, entirely disproportionate to any apparent cause. It may be as marked as that of carcinoma, and, indeed, the disease has been called cachexia exophthalmica. In many cases, however, the patient is rosy and well nourished.

The disease may be incomplete, one or more cardinal symptoms being absent. These are the masked forms, the "formes frustes." Most frequently it runs a slow, progressive course. More rarely it is acute, and rapidly fatal. F. Mueller reported some very interesting, acute cases in 1893.

To account for these various symptoms, numerous theories have been advanced. Only three are, at present, well supported: 1. That it is a pure neurosis. 2. That it is due to a central (medullary) lesion. 3. That it is due to an increased, perhaps perverted function of the thyroid gland.

The arguments in favor of the neurosis theory are these:

1. The frequent neuropathic family and personal history.

2. The onset with emotion. H. Mackenzie especially calls attention to the facies being but an exaggeration of the physiological facies of fright; protuding eyes, flushed face, tremor, palpitation, and swelling of the throat.

3. The frequent association with hysteria, epilepsy and chorea.

4. The absence of any lesion to account for it.

5. The cases cured by operation on the nose. These

are reported by Hopmann, Hack and Frænkel. A minor operation on the nose has been followed by amelioration or disappearance of the symptoms. The very small number of cases precludes any definite conclusion. Many cases have had their nasal passages treated without any result whatsoever on the disease.

Against these may be urged that the meagre pathological testimony may be due to lack of skill. (Moebius remarks that in strychnia poisoning there is no definite lesion). The mortality is too high and the acute cases totally unlike a pure neurosis. Again, a patient's statements as to the cause of onset are always to be looked on with suspicion. It is notorious how frequently anterior poliomyelitis is attributed to a fall, and chorea to a fright.

The theory of a central lesion has been supported by Mendel, Hale White and others. Mendel's pupil, Mannheim, in his work on exophthalmic goitre, sums up the arguments in favor of this as follows: He first premises that all the symptoms could be explained by bulbar lesions. Besides this there are, pointing to the medulla as the seat of the disease.

1. The severe course of exophthalmic goitre, and its combination with other spinal cord diseases and with diabetes.

2. The experiments. This refers to Filehne's, Durdufi's, and Bienfalt's work. Filehne incised the grey matter of the upper part of the restiform body and had exophthalmos and tachycardia. On electrical stimulation he also had goitre at times. Durdufi repeated this, and incised also the tub. acustica, getting Stellwag's sign. Bienfalt practically confirmed Filehne's experiments.

3. The pathological anatomy. Several observers have found more or less hæmorrhage into the floor of the fourth ventricle. Hale White noted an old superficial hæmorrhage extending from the middle line to the corpus restiforme, and involving the sixth nucleus on one side. Mendel found one restiform body smaller than the other, and the right solitary fasciculus atrophied. At the time Mendel's paper was presented Oppenheim remarked that the corpora restiforma are normally so unlike, that a slight difference in size would have but little weight.

In most autopsies, however, the central nervous system has been negative, and in Mueller's acute cases only slight, recent hæmorrhages were seen. Mannheim explains this by our poor methods of demonstration.

Finally we have the thyroid theory, led by Moebius, in Germany, Joffroy, in France, and Greenfield and Byrom Bramwell, in Scotland. The arguments for this may be stated as follows:

1. Morbid anatomy. In all autopsies some changes have been observed in the thyroid gland, and frequently these have been in the direction of functional hyperplasia. In some cases, however, (notably Hektoen's) the gland was almost completely fibrous.

2. The action of thyroid extract. Soon after the discovery of thyroid therapy for myxœdema, Murray, and later others, warned against the effects of overdosage. These were, notably, tachycardia, tremor, headache, sweating, prostration and anorexia, diarrhœa and polyuria. In the *Soc. des Hôp.*, on October 12, 1894, Beclère reported a case in which exophthalmos developed after an overdose of thyroid. Finally, in the *Soc. des Hôp.*, on November 10, 1894, Ballet and Enriguez report experiments on a dog, injecting thyroid extract. The dog had two courses, and in each developed goitre, which diminished and disappeared when the injections were omitted.

3. The usual effect of thyroid administration in exophthalmic goitre is to increase the symptoms. There are exceptions to this, however.

4. The most successful line of treatment, so far, is that tending to diminish the bulk of the goitre. Out of sixty-eight operations on record, eighteen completely recovered; in twenty-six there was more or less improvement; nine showed no change; in five death was almost immediate,[10] and in four death occurred within twenty-four hours. In four cases there was apparent cure, but the symptoms returned, and in two cases the operation was followed by tetany. This makes about fifty per cent. improved by the operation, and a mortality of about fifteen per cent. This supposes that all these cases reported were true exophthalmic goitre, which has been questioned by several writers.

5. The striking contrast of symptoms between exophthalmic goitre and myxœdema, as pointed out by Moebius. This is well shown in the two sisters whose histories were given above.

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[10] One of these fatal cases was in this hospital.

	Miss A., *æt.* 19.	Mrs. E., *æt.* 37.
Pulse,	100 to 120.	58 to 70.
Heart,	Impulse heaving; apex in sixth; first sound loud.	Negative.
Eyes,	Prominent (no v. Graefe's sign).	Not prominent.
Thyroid,	Symmetrically enlarged.	Not to be made out
Tremor,	Present.	Absent.
Skin,	Moist; sweats.	Dry and harsh.
Face,	Flushed; red patches on cheeks.	Heavy, full, uniform color.
Temperament,	Emotional and neurotic.	Apathetic and heavy.
Weight,	137.	189.
Thyroid treatment,	Had to be omitted because of increase in symptoms.	Resulted in steady improvement,

6. Finally, the course of the disease is more like an intoxication. It is probable that the chief brunt of the toxæmia falls on the central nervous system, and this would give rise to medullary symptoms without marked lesions.

The question might possibly be cleared up by injecting animals with extract of thyroid from an exophthalmic goitre subject. This disease has been observed once in a cow, in a horse, and in a dog, so that they are susceptible to it,